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HIGH PRODUCTION VOLUME (HPV)

CHEMICAL INITIATIVE

FINAL SUBMISSION

For

DITHIOPHOSPHATE ALKYL ESTERS CATEGORY

**Prepared by
The American Chemistry Council
Petroleum Additives Panel
Health, Environmental and Regulatory Task Group**

December 2005

**LIST OF MEMBER COMPANIES IN THE
HEALTH, ENVIRONMENTAL AND REGULATORY TASK GROUP**

The Health, Environmental, and Regulatory Task Group (HERTG) of the American Chemistry Council Petroleum Additives Panel includes the following member companies:

Afton Chemical Corporation (formerly Ethyl Corporation)

Chevron Oronite Company, LLC

ExxonMobil Chemical Company

Infineum

The Lubrizol Corporation

SNPE

EXECUTIVE SUMMARY

The American Chemistry Council Petroleum Additives Panel Health, Environmental and Regulatory Task Group (HERTG), and its member companies, hereby submit for review this Final Submission for the “*Dithiophosphate Alkyl Esters*” category of chemicals under the United States Environmental Protection Agency High Production Volume (HPV) Chemical Challenge Program. This final submission should be read in its entirety in order to obtain a complete understanding of the category and fulfilled testing requirements.

Dithiophosphate Alkyl Esters Category. Relying on several factors specified in EPA’s guidance document on “Development of Chemical Categories in the HPV Challenge Program,” in which use of chemical categories is encouraged, the following nine closely related chemicals constitute a chemical category:

- Phosphorodithioic acid, mixed O,O-bis (1,3-dimethylbutyl and iso-propyl) esters – (CAS # 84605-28-7), referred to as “mixed 1,3-dimethylbutyl and iso-propyl derivative”
- Phosphorodithioic acid, mixed O,O-bis(iso-butyl and pentyl) esters – (CAS # 68516-01-8), referred to as “mixed isobutyl and pentyl derivative”
- Phosphorodithioic acid, mixed O,O-bis(sec-butyl and 1,3 dimethylbutyl) esters – (CAS # 68784-30-5), referred to as “mixed sec-butyl and 1,3-dimethylbutyl derivative”
- Phosphorodithioic acid mixed O,O-bis(sec-butyl and isooctyl) mixed esters – (CAS # 113706-14-2), referred to as “mixed sec-butyl and isooctyl derivative”
- Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and iso-butyl) esters – (CAS # 68784-32-7), referred to as “mixed 2-ethylhexyl and isobutyl derivative”
- 2-Pentanol, 4-methyl-hydrogen phosphorodithioate – (CAS # 6028-47-3), referred to as “1,3-dimethylbutyl derivative”
- Phosphorodithioic acid, O,O-bis(2-ethylhexyl) esters – (CAS# 5810-88-8), referred to as “2-ethylhexyl derivative”
- Phosphorodithioic acid, O,O-dioctyl ester, branched – (CAS# 68649-43-4), referred to as “branched isooctyl derivative”
- Phosphorodithioic acid, O,O-diisooctyl ester – (CAS# 26999-29-1), referred to as “isooctyl derivative”.

An additional chemical that is not a part of the HPV Challenge Program but which is an analogue of these chemicals and fits into the Dithiophosphate alkyl esters category was used in the data review: Phosphorodithioic acid, mixed O,O-bis(iso-Bu and isooctyl and pentyl) esters. The alkyl chains in this derivative (C4-C8) are within the range of the nine chemicals in the HPV category (C3-C8). This analogue has no CAS# because the substance was originally nominated as confidential to the U.S. TSCA Inventory and will be referred to as “mixed isobutyl, isooctyl and pentyl derivative”.

Structural Similarity. A key factor supporting the classification of these chemicals as a category is their structural similarity. All substances in this category consist of a phosphorodithioic acid structure with alkyl ester substituent groups.

Fate and Transport Characteristics. Based on biodegradation test data for two members of the zinc dialkyldithiophosphate category, members of this category are expected to be poorly biodegradable. The members of the category are resistant to hydrolysis at room temperature because they lack readily hydrolyzable moieties. One member of this category was shown to be stable with respect to hydrolysis at room temperature. This makes hydrolysis modeling unnecessary and no further hydrolysis testing was conducted for this category. Photodegradation is not expected to cause significant physical degradation of Dithiophosphate alkyl esters. However, computer-modeled data was developed to adequately characterize the potential atmospheric oxidation for members of this category. Although these substances are not expected to partition to water or air if released into the environment due to their low water solubility and low vapor pressure, computer-modeled environmental partitioning data is calculated on the members of this category.

Aquatic Toxicity. The 96-hour LL_{50} for the rainbow trout (*Oncorhynchus mykiss*) exposed to the mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS # 84605-28-7) is greater than 100 mg/l loading rate WAF (Water Accommodated Fractions) and the No Observed Effect Loading rate (NOEL) is 100 mg/l loading rate WAF. The 48-h EL_{50} for *Daphnia magna* exposed to the mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS # 84605-28-7) is 36 mg/l loading rate WAF. The 72-hour E_bL_{50} for the green alga (*Scenedesmus subspicatus*) exposed to the mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS # 84605-28-7) is 55 mg/l loading rate WAF; the E_rL_{50} (0-72 h) is 87 mg/l loading rate WAF and the NOEL is 25 mg/l loading rate WAF. These data are bridged to other members of the category.

Mammalian Toxicity. Acute mammalian toxicity tests are available on a lower molecular weight analogue for this category. The molecular weight range of this category is fairly narrow (C3-C8) and the alkyl groups similar. Bridging is used to all Dithiophosphate alkyl esters based on the C3-C8 Dithiophosphate Ester analogue derivative data. Dithiophosphate alkyl esters are extremely corrosive to tissue; there is low risk of human exposure and test animals will experience extreme pain and suffering with additional testing. Therefore, in order to minimize stress to test animals, no repeat dose or reproductive/developmental testing was considered necessary.

Genotoxicity. An *in vitro* bacterial gene mutation assay was conducted for the mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS # 84605-28-7). This substance does not demonstrate mutagenic activity in either the presence or absence of metabolic activation. The *in vitro* chromosomal aberration assay on the mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS # 84605-28-7) showed that this substance is non-clastogenic to human lymphocytes *in vitro*. This derivative is the lowest molecular weight component of this category and hence represents the "worst case" genetic toxicity of the chemicals in this category. Therefore, data from this substance is bridged to other members of the category.

Conclusion. Based on the physiochemical, environmental fate, aquatic toxicology and mammalian toxicology studies completed for this submission and the data reviewed, the HERTG concludes that the Dithiophosphate alkyl esters do not readily pose a risk to the aquatic and mammalian environments. As this final submission was completed, careful consideration was given to the number of animals required for tests and conditions to which the animals would be exposed.

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1.0 INTRODUCTION

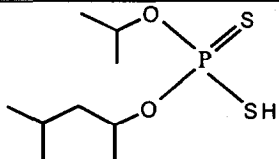
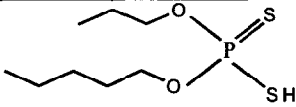
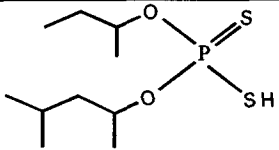
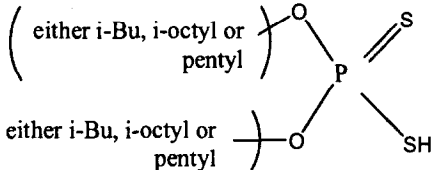
In March 1999, the American Chemistry Council (formerly the Chemical Manufacturers Association) Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG), and its participating member companies committed to address certain chemicals listed under the Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program. This final submission follows up on that commitment.

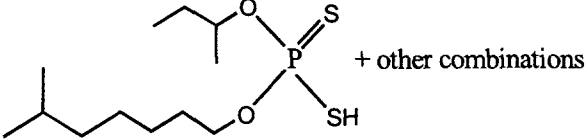
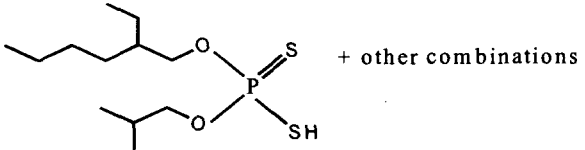
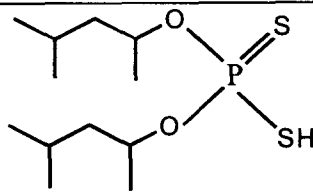
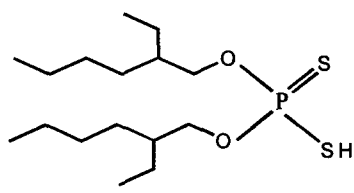
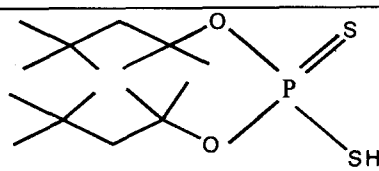
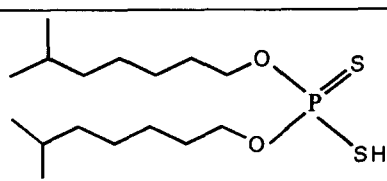
Specifically, this final submission illustrates how the HERTG addressed testing requirements for the following nine substances (structures are representative in Table 1):

- Phosphorodithioic acid, mixed O,O-bis (1,3-dimethylbutyl and iso-propyl) esters – (CAS # 84605-28-7), referred to as “mixed 1,3-dimethylbutyl and iso-propyl derivative”
- Phosphorodithioic acid, mixed O,O-bis(iso-butyl and pentyl) esters – (CAS # 68516-01-8), referred to as “mixed isobutyl and pentyl derivative”
- Phosphorodithioic acid, mixed O,O-bis(sec-butyl and 1,3 dimethylbutyl) esters – (CAS # 68784-30-5), referred to as “mixed sec-butyl and 1,3-dimethylbutyl derivative”
- Phosphorodithioic acid mixed O,O-bis(sec-butyl and isooctyl) mixed esters – (CAS # 113706-14-2), referred to as “mixed sec-butyl and isooctyl derivative”
- Phosphorodithioic acid, mixed 0,0-bis(2-ethylhexyl and iso-butyl) esters – (CAS # 68784-32-7), referred to as “mixed 2-ethyl hexyl and isobutyl derivative”
- 2-Pentanol, 4-methyl-hydrogen phosphorodithioate – (CAS # 6028-47-3), referred to as “1,3-dimethylbutyl derivative”
- Phosphorodithioic acid, 0,0-bis(2-ethylhexyl) esters – (CAS# 5810-88-8), referred to as “2-ethylhexyl derivative”
- Phosphorodithioic acid, O,O-dioctyl ester, branched – (CAS# 68649-43-4), referred to as “branched isooctyl derivative”
- Phosphorodithioic acid, O,O-diisooctyl ester – (CAS# 26999-29-1), referred to as “isooctyl derivative”

An additional chemical (Phosphorodithioic acid, mixed O,O-bis(iso-Bu and isooctyl and pentyl) esters) is used in the data review. This chemical is not a part of the HPV Challenge Program but is an analogue of these chemicals and fits into the Dithiophosphate alkyl esters category. The alkyl chain in this derivative (C4-C8) is within the range of the nine chemicals in the HPV category (C3-C8). This analogue has no CAS# and will be referred to as “mixed C3-C8 Dithiophosphate Ester analogue derivative”.

TABLE 1
CHEMICAL STRUCTURES AND CAS NUMBERS OF DITHIOPHOSPHATE AKLY
ESTER CATEGORY MEMBERS
(In estimated lowest to highest molecular weight order)

CAS #	Structure	Simplified Chemical Name
84605-28-7	 + other combinations Phosphorodithioic acid, mixed O,O-bis (1,3-dimethylbutyl and iso-propyl) esters	mixed 1,3-dimethylbutyl and iso-propyl derivative
68516-01-8	 + other combinations Phosphorodithioic acid, mixed O,O-bis(iso-butyl and pentyl) esters	mixed isobutyl and pentyl derivative
68784-30-5	 + other combinations Phosphorodithioic acid, mixed O,O-bis(sec-butyl and 1,3-dimethylbutyl) esters	mixed sec-butyl and 1,3-dimethylbutyl derivative
mixed isobutyl, isooctyl and pentyl derivative (NO CAS #)	 Phosphorodithioic acid, mixed O,O-bis(iso-Bu and isooctyl and pentyl) esters	mixed isobutyl, isooctyl and pentyl derivative

113706-14-2	 <p>Phosphorodithioic acid mixed O,O-bis(sec-butyl and isooctyl) mixed esters</p>	mixed sec-butyl and isooctyl derivative
68784-32-7	 <p>Phosphorodithioic acid, mixed O,O-bis(2-ethylhexyl and isobutyl) esters</p>	mixed 2-ethyl hexyl and isobutyl derivative
6028-47-3	 <p>2-Pentanol, 4-methyl-hydrogen phosphorodithioate</p>	1,3-dimethylbutyl derivative
5810-88-8	 <p>Phosphorodithioic acid, O,O-bis(2-ethylhexyl) esters</p>	2-ethylhexyl derivative
68649-43-4	 <p>Phosphorodithioic acid, O,O-dioctyl ester, branched</p>	branched isooctyl derivative
26999-29-1	 <p>Phosphorodithioic acid, O,O-diisooctyl ester</p>	isooctyl derivative

The only structural variable that influences the molecular weight of the category members and consequently their bioavailability and toxicity is the length of the alkyl side chain, which may vary from C3 to C8. The length and extent of branching of the alkyl side chain also affects the water solubility of these substances.

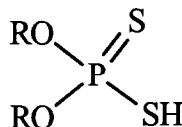
In preparing this final submission the following steps have been undertaken:

Step 1: A review of the literature and confidential company data was conducted on the physiochemical properties, mammalian toxicity endpoints and environmental fate and effects for the nine dithiophosphate alkyl esters derivatives in this category. Searches included the following sources: MEDLINE, BIOSIS, CANCERLIT, CAPLUS, CHEMLIST, EMBASE, HSDB, RTECS, EMIC, and TOXLINE databases; the TSCATS database for relevant unpublished studies on these chemicals; and standard handbooks and databases (e.g., Sax, CRC Handbook on Chemicals, IUCLID, Merck Index, and other references) for physiochemical properties.

Step 2: The compiled data was evaluated for adequacy in accordance with the EPA guidance documentation. Where additional data was needed, testing was completed to fulfill the Screening Information Data Sets requirements.

2.0 GENERAL SUBSTANCE INFORMATION

Dithiophosphate alkyl esters consist of a phosphorodithioic acid structure with alkyl ester substituent groups. The alkyl groups are saturated hydrocarbon chains that vary in length and extent of branching. An idealized structure is below:



The chemical structures and CAS numbers for the members of the Dithiophosphate Esters category and analogue chemical are presented in Table 1 and the chemical names in Table 2. These substances are prepared by reacting phosphorous pentasulfide with one or more primary or secondary alcohols to form the phosphorodithioic acid ester. Residual phosphorus pentasulfide is removed and stored as a closed system intermediate. These esters are not transported to other sites but are converted to the commercial zinc dialkyldithiophosphates in a subsequent in-line step at the same manufacturing site.

2.1 Exposure Information

Dithiophosphate alkyl esters are closed system intermediates. They are used by the member companies of the HERTG to produce components for lubricating oils by subsequent neutralization to form metal salts such as zinc dialkyldithiophosphates. In all HERTG manufacturing sites in the United States, these materials are neutralized in the reaction vessel in which they are produced or stored in on-site facilities until neutralized.

They are not transported to other manufacturing sites by members of the HERTG. Since the neutralization reactions that are used to produce the lubricating oil components use an excess of metal oxide or hydroxide, dithiophosphate alkyl esters are not present in any end products at analytically detectable concentrations. Therefore, under prescribed conditions of use, the potential for exposure to the environment or to humans is extremely low.

3.0 PHYSICOCHEMICAL PROPERTIES

Selected physicochemical properties of the members of the Dithiophosphate alkyl esters category are presented in Table 3. The members of this category are all amber colored viscous liquids at ambient temperature. The physicochemical properties of these substances, which are described below, are very similar as would be expected based upon the similarity in their chemical structures. All members of this category are within a narrow molecular weight range (256 - 354 daltons) and are highly acidic. In addition, based on modeling data, they have similar melting and boiling points, low water solubility, low vapor pressure and are lipophilic in nature. These properties provide support to the justification of this group of chemicals as a category within the HPV Challenge Program.

3.1 Molecular Weight and Alkyl Side Chain Length

The members of the category range in molecular weight from 256 to 354 daltons (Table 3).

3.2 pH

Dithiophosphate alkyl esters are strong acids. This acidity makes the members of this category corrosive.

3.3 Boiling Point

The Dithiophosphate alkyl esters differ only in the alkyl chain(s) present in the molecule. Therefore, the boiling points generally follow a pattern based upon their molecular weight and the extent of branching of the alkyl side chain. Modeling data indicates that the boiling point of these substances could range from 289 to 385°C (Table 3).

3.4 Vapor Pressure

Modeling data indicates that the vapor pressure of these substances range from 3.46×10^{-3} to 1.9×10^{-5} mm Hg at 25°C and generally follow a pattern based upon their molecular weight and the extent of branching of the alkyl side chain (Table 3).

3.5 Water Solubility

The low water solubility is consistent with the high lipophilic nature of these substances. The category member containing the shortest alkyl chain, mixed 1,3-dimethylbutyl and isopropyl derivative (CAS# 84605-28-7) was tested for water solubility and was determined to be 19.6 g/l of solution with a nominal loading rate of 100 g/l at 20.0 ± 0.5 °C.

3.6 Octanol Water Coefficient

Modeling data indicates that these substances have low water solubility and that the log of the octanol-water partition coefficient (log $K_{o/w}$) of these substances range from 4.48 to 7.99 (Table 3).

TABLE 2
PHYSICOCHEMICAL PROPERTIES OF DITHIOPHOSPHATE ALKYL ESTERS

CAS Number	Molecular Weight	MP ¹ °C	BP ¹ °C	Vapor Pressure mm Hg ¹	Water Solubility mg/L ¹	Log K _{ow} ¹
84605-28-7	256	-39	289	0.00346	3.277	4.48
68516-01-8	256	-18	307	0.00134	2.454	4.62
68784-30-5	270	-29	304	0.00157	1.04	4.97
113706-14-2	298	0	339	0.000246	0.08998	6.02
68784-32-7	298	0	339	0.000246	0.08998	6.02
6028-47-3	298	-19	323	0.00056	0.1201	5.88
5810-88-8	354	-13	385	1.9×10^{-5}	0.0008768	7.99
68649-43-4	354	16	353	0.000113	0.001573	7.69
26999-29-1	354	-13	385	1.9×10^{-5}	0.0008768	7.99

¹Data derived from modeling

4.0 ENVIRONMENTAL FATE DATA

4.1 Biodegradability

Adequate biodegradation data existed for two of twelve substances in the zinc dialkyldithiophosphate category including the lowest molecular weight (CAS# 84605-29-8) and the highest molecular weight (CAS# 54261-67-5) members. These data are similar and indicate a narrow range of biodegradability irrespective of molecular weight and alkyl chain type. The hydrocarbon portion of these compounds that is susceptible to biodegradation is present in both the zinc dialkyldithiophosphates and the dithiophosphate alkyl esters. It is expected that the dithiophosphate alkyl esters would behave similarly to the corresponding zinc derivatives. Therefore, data from the zinc dialkyldithiophosphate category is bridged to the members of the dithiophosphate alkyl esters category.

4.2 Hydrolysis

The members of the category are resistant to hydrolysis at room temperature because they lack readily hydrolyzable moieties.

Adequate data exists on hydrolytic evaluations on the 2-ethylhexyl derivative (CAS# 5810-88-8) member of the Dithiophosphate alkyl esters category performed at room

temperature and at 80 degrees C. At room temperature, hydrolysis does not readily occur. When heated to 80 degrees C, hydrolytic degradation results in the formation of the phosphorothioic acid ester and hydrogen sulfide. Continued heating at high temperatures results in the formation of the mono-ester and eventually, phosphorothioic acid itself.

Data from the 2-ethylhexyl derivative (CAS# 5810-88-8) is used to bridge to the other members of the category.

4.3 Photodegradation

The Atmospheric Oxidation Potential (AOP) for category members was evaluated using the modeling program AOPWIN. The AOP data for representative structures of the category was evaluated to estimate (1) rate constants for the atmospheric, gas phase reaction as mediated by photochemically produced hydroxyl radicals and (2) atmospheric half-lives based on hydroxyl radical attack. The data is presented in Table 4.

4.4 Fugacity

The relative distribution of substances within this category among environmental compartments was evaluated using a Level III fugacity model. Data developed using this model can be used for simple comparative purposes across several substances. The data presented in Table 5 indicate the likely environmental compartment into which a chemical will tend to partition and an indication of the distribution in each medium.

TABLE 3
EVALUATION OF ENVIRONMENTAL FATE DATA FOR DITHIOPHOSPHATE
ALKYL ESTERS CATEGORY MEMBERS

CAS Number	BIODEGRADABILITY	HYDROLYSIS	PHOTODEGRADATION
	Available Data & Testing	Available Data & Testing	Available Data & Testing
84605-28-7	Bridging ¹	Bridging ²	<u>Direct Photodegradation:</u> Dithiophosphate alkyl esters are not subject to photolytic reactions <u>Indirect Photodegradation:</u> Calculated OH ⁻ Rate Constant (cm ³ /molec-sec) = 146.3228 E-12 Calculated Half-life in Air (hrs) = 0.877 Hrs
68516-01-8	Bridging ¹	Bridging ²	<u>Direct Photodegradation:</u> Dithiophosphate alkyl esters are not subject to photolytic reactions <u>Indirect Photodegradation:</u> Calculated OH ⁻ Rate Constant (cm ³ /molec-sec) = 105.5599 E-12 Calculated Half-life in Air (hrs) = 1.216 Hrs
68784-30-5	Bridging ¹	Bridging ²	<u>Direct Photodegradation:</u> Dithiophosphate alkyl esters are not subject to photolytic reactions <u>Indirect Photodegradation:</u> Calculated OH ⁻ Rate Constant (cm ³ /molec-sec) = 156.6187 E-12 Calculated Half-life in Air (hrs) = 0.820
113706-14-2	Bridging ¹	Bridging ²	<u>Direct Photodegradation:</u> Dithiophosphate alkyl

			<p>esters are not subject to photolytic reactions</p> <p><u>Indirect Photodegradation:</u> Calculated OH⁻ Rate Constant (cm³/molec-sec) = 135.3242 E-12 Calculated Half-life in Air (hrs) = 0.948 Hrs</p>
68784-32-7	Bridging ¹	Bridging ²	<p><u>Direct Photodegradation:</u> Dithiophosphate alkyl esters are not subject to photolytic reactions</p> <p><u>Indirect Photodegradation:</u> Calculated OH⁻ Rate Constant (cm³/molec-sec) = 111.8908 E-12 Calculated Half-life in Air (hrs) = 1.147 Hrs</p>
6028-47-3	Bridging ¹	Bridging ²	<p><u>Direct Photodegradation:</u> Dithiophosphate alkyl esters are not subject to photolytic reactions</p> <p><u>Indirect Photodegradation:</u> Calculated OH⁻ Rate Constant (cm³/molec-sec) = 159.4364 E-12 Calculated Half-life in Air (hrs) = 0.805 Hrs</p>
5810-88-8	Bridging ¹	Does not readily occur	<p><u>Direct Photodegradation:</u> Dithiophosphate alkyl esters are not subject to photolytic reactions</p> <p><u>Indirect Photodegradation:</u> Calculated OH⁻ Rate Constant (cm³/molec-sec) = 118.2384 E-12 Calculated Half-life in Air (hrs) = 1.086 Hrs</p>
68649-43-4	Bridging ¹	Bridging ²	<p><u>Direct Photodegradation:</u> Dithiophosphate alkyl</p>

			<p>esters are not subject to photolytic reactions</p> <p><u>Indirect Photodegradation:</u> Calculated OH⁻ Rate Constant (cm³/molec-sec) = 57.4989 E-12 Calculated Half-life in Air (hrs) = 2.232 Hrs</p>
26999-29-1	Bridging ¹	Bridging ²	<p><u>Direct Photodegradation:</u> Dithiophosphate alkyl esters are not subject to photolytic reactions</p> <p><u>Indirect Photodegradation:</u> Calculated OH⁻ Rate Constant (cm³/molec-sec) = 116.8475 E-12 Calculated Half-life in Air (hrs) = 1.098 Hrs</p>

¹Bridging from zinc dialkyldithiophosphates category data.

²Bridging from CAS# 5810-88-8 data.

TABLE 4
DISTRIBUTION DATA FOR SELECTED CHEMICAL COMPONENTS FOR
DITHIOPHOSPHATE ALKYL ESTERS CATEGORY MEMBERS

CAS Number	PERCENT DISTRIBUTION			
	Air (%)	Water (%)	Soil (%)	Sediment (%)
84605-28-7	0.135	8.75	84.9	6.27
68516-01-8	0.389	16	80.4	3.22
68784-30-5	0.107	7.39	76.7	15.8
113706-14-2	0.0576	3.52	43.2	53.2

68784-32-7	0.161	6.76	42.5	50.6
6028-47-3	0.0557	3.95	47.2	48.8
5810-88-8	0.0823	3.79	28.2	67.9
68649-43-4	0.0196	0.767	39.7	59.5
26999-29-1	0.0334	1.92	28.2	69.8

5.0 AQUATIC TOXICITY DATA

5.1 Fish Acute Toxicity

An acute toxicity test with Rainbow trout (*Oncorhynchus mykiss*) was conducted with the mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS# 84605-28-7). The 96-hour LL₅₀ based on nominal loading rates was greater than 100 mg/l loading rate WAF and correspondingly the No Observed Effect Loading rate was 100 mg/l loading rate WAF.

5.2 Invertebrate Acute Toxicity

An acute invertebrate toxicity test with *Daphnia magna* was conducted with the mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS# 84605-28-7). A 48-h EL₅₀ based on nominal loading rates was 36 mg/L loading rate WAF. The No Observed Effect Loading rate was 18 mg/l loading rate WAF.

5.3 Alga Acute Toxicity

An algal inhibition test was conducted to assess the effect of the mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS# 84605-28-7) on the growth of the green alga *Scenedesmus subspicatus*. The 72-h E_bL₅₀ was 55 mg/l loading rate WAF and the E_tL₅₀ (0-72 h) was 87 mg/l loading rate WAF. The No Observed Effect Loading rate was 25 mg/l loading rate WAF.

TABLE 5
AQUATIC TOXICITY DATA FOR DITHIOPHOSPHATE ALKYL ESTERS
CATEGORY MEMBERS

CAS Number	ACUTE TOXICITY TO FISH	ACUTE TOXICITY TO INVERTEBRATES	TOXICITY TO ALGAE
	Available data	Available data	Available data
84605-28-7	96-hr LL ₅₀ > 100 mg/l	48-hr EL ₅₀ = 36 mg/L	72-hr E _b L ₅₀ = 55 mg/l
68516-01-8	Bridging ¹	Bridging ¹	Bridging ¹
68784-30-5	Bridging ¹	Bridging ¹	Bridging ¹
113706-14-2	Bridging ¹	Bridging ¹	Bridging ¹
68784-32-7	Bridging ¹	Bridging ¹	Bridging ¹
6028-47-3	Bridging ¹	Bridging ¹	Bridging ¹
5810-88-8	Bridging ¹	Bridging ¹	Bridging ¹
68649-43-4	Bridging ¹	Bridging ¹	Bridging ¹
26999-29-1	Bridging ¹	Bridging ¹	Bridging ¹

¹Bridging from CAS# 84605-28-7 data.

6.0 MAMMALIAN TOXICOLOGY DATA

6.1 Acute Mammalian Toxicity

Acute mammalian toxicity tests were available on a lower molecular weight analogue for this category (Mixed isobutyl, isooctyl and pentyl derivative). The molecular weight range of this category is fairly narrow (C3-C8) and the alkyl groups similar. Therefore, the acute toxicity was not expected to vary greatly. Due to the corrosivity of these chemicals, as seen in the eye and skin irritation studies, to spare animals from unnecessary pain and suffering, no additional acute mammalian toxicity testing was conducted on the Dithiophosphate alkyl esters category constituents. Bridging was used to all Dithiophosphate alkyl esters based on the C3-C8 Dithiophosphate Ester analogue derivative data.

6.2 Repeated Dose Toxicity and Reproductive/Developmental Toxicity

The exposure profile of Dithiophosphate alkyl esters offers assurance that there is minimal risk for repeated dose toxicity. The exposure potential to production workers is very low due to process, engineering and personal protection equipment controls. For concentrated component, the only practical type of exposure would be acute and only occur in the rare case of an accidental spill. The dermal route would be the principle route of exposure. Oral or inhalation exposure is expected to be rare.

Additionally, Dithiophosphate alkyl esters are corrosive. Therefore, the handling and storage conditions lead to a limited potential for long-term exposure. Since exposures resulting from chemical accidents are likely to be of relatively short versus chronic duration, repeated-dose toxicity, developmental or reproduction/developmental toxicity testing was not conducted.

In addition to the arguments outlined above, HERTG believes that additional testing of Dithiophosphate alkyl esters will cause unnecessary distress to experimental animals since previously conducted experimental studies demonstrate Dithiophosphate alkyl esters are corrosive to skin, eye and mucosal membranes.

Based on scientific review and the limited potential for intentional or accidental human exposure, the sponsoring companies of HERTG would be unable to conduct additional mammalian toxicity testing on Dithiophosphate alkyl esters without imparting unnecessary distress and suffering to the experimental animal. The HERTG believes that by not conducting mammalian toxicity tests on chemicals known to be corrosive and that have limited risk of exposure to the environment and to humans, we are supporting the spirit of this commitment.

TABLE 6
EVALUATION OF ACUTE MAMMALIAN TOXICOLOGY OF DITHIOPHOSPHATE
ALKYL ESTERS

CAS Number	ACUTE ORAL TOXICITY ¹	ACUTE DERMAL TOXICITY ¹	ACUTE INHALATION TOXICITY ²	PRIMARY DERMAL IRRITATION	EYE IRRITATION
	Available Data & Testing	Available Data & Testing	Available Data & Testing	Available Data	Available Data
84605-28-7	Bridging	Bridging	Bridging		
68516-01-8	Bridging	Bridging	Bridging		
68784-30-5	Bridging	Bridging	Bridging		
mixed isobutyl, isooctyl and pentyl derivative	Bridging	>2,000 mg/kg	>0.198 mg/L (nominal concentration)	Severe damage to the skin. Edema, erythema and/or eschar formation was observed at the test sites of all rabbits at all scoring intervals. Necrosis was evident on days 1, 3, and 7 following chemical application. The primary dermal irritation score was 8.0/8.0.	Maximum irritation score of 78.5/110.0 (day 1). All rabbits exhibited eye irritation and recovery was not complete in any rabbit by day 21. One rabbit euthanized at day 14 due to the severe ocular reaction.
113706-14-2	Bridging	Bridging	Bridging		
68784-32-7	Bridging	Bridging	Bridging		
6028-47-3	Bridging	Bridging	Bridging		
5810-88-8	2140 ml/kg ³	1250 ml/kg ³	Bridging		
68649-43-4	Bridging	Bridging	Bridging		
26999-29-1	Bridging	Bridging	Bridging		

¹Toxicity endpoints are expressed as median lethal dose (LD₅₀) for dermal toxicity.

²Toxicity of endpoint is expressed as median lethal concentration (LD₅₀) for inhalation toxicity

³Smyth, Henry F., Charles P. Carpenter, Carrol S. Weil, Urbano C. Pozzani, and Jean A. Striegel. "Range-Finding Toxicity Data: List VI." American Industrial Hygiene Association Journal 1962. 23:95.

6.3 GENOTOXICITY

6.3.1 Bacterial Gene Mutation Assay

An *in vitro* bacterial gene mutation assay was conducted for the mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS # 84605-28-7). This substance does not demonstrate mutagenic activity in either the presence or absence of metabolic activation. This derivative is the lowest molecular weight component of this category and hence represents the “worst case” genetic toxicity of the chemicals in this category. Therefore data from this substance is bridged to other members of the category (Table 7).

6.3.2 Chromosome Aberration Assay

The *in vitro* chromosomal aberration assay on the mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS # 84605-28-7) showed that the material was non-clastogenic to human lymphocytes *in vitro*. This derivative is the lowest molecular weight component of this category and hence represents the “worst case” genetic toxicity of the chemicals in this category. Therefore data from this substance was bridged to other members of the category.

TABLE 7
EVALUATION OF GENOTOXICITY OF DITHIOPHOSPHATE ALKYL ESTERS

CAS Number	GENE MUTATION ASSAY	CHROMOSOMAL ABERRATION ASSAY
84605-28-7	<i>In vitro</i> Bacterial Reverse Mutation Assay – With and Without S-9 – Not Mutagenic	<i>In vitro</i> Chromosome Aberration Assay in Human Lymphocytes– Non-Clastogenic
68516-01-8	Bridging ¹	Bridging ¹
68784-30-5	Bridging ¹	Bridging ¹
113706-14-2	Bridging ¹	Bridging ¹
68784-32-7	Bridging ¹	Bridging ¹
6028-47-3	Bridging ¹	Bridging ¹
5810-88-8	Bridging ¹	Bridging ¹
68649-43-4	Bridging ¹	Bridging ¹

CAS Number	GENE MUTATION ASSAY	CHROMOSOMAL ABERRATION ASSAY
26999-29-1	Bridging ¹	Bridging ¹
¹ Bridging from CAS #84605-28-7		

TABLE 8
SUMMARY OF DATA FOR DITHIOPHOSPHATE ALKYL ESTERS

CAS Number	Environmental Fate					Ecotoxicity			Human Health Effects				
	Physical Chem	Photodeg	Hydrolysis	Fugacity	Biodeg	Acute Fish Toxicity	Acute Invert Toxicity	Algal Toxicity	Acute Toxicity	Point Mutations	Chrom Effects	Sub-chronic	Repro/Develop
84605-28-7	A	C	B	C	B	A	A	A	B	A	A	I	I
68516-01-8	A	C	B	C	B	B	B	B	B	B	B	I	I
68784-30-5	A	C	B	C	B	B	B	B	B	B	B	I	I
113706-14-2	A	C	B	C	B	B	B	B	B	B	B	I	I
68784-32-7	A	C	B	C	B	B	B	B	B	B	B	I	I
6028-47-3	A	C	B	C	B	B	B	B	B	B	B	I	I
5810-88-8	A	C	A	C	B	B	B	B	A	B	B	I	I
68649-43-4	A	C	B	C	B	B	B	B	B	B	B	I	I
26999-29-1	A	C	B	C	B	B	B	B	B	B	B	I	I

A Adequate data available
 C Computer modeling
 B Bridging
 I Inappropriate due to corrosivity of chemical and risk and exposure analysis